

09/806370  
Rec'd PCT/PTO 28 MAR 2001

Wyeth



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DFW/aja  
19 April 2000

BY FAX

The European Patent Office  
D-80298  
MUNCHEN  
Germany

Dear Sirs

RE: Chapter II  
International Application No PCT US99/22520  
Filed 30 September 1999  
American Cyanamid Company Case ACY-33383

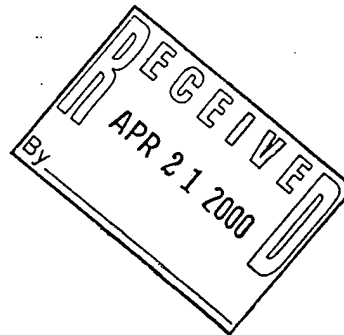
I file herewith the Demand under Article 31 of the Patent Co-operation Treaty requesting that the International Preliminary Examination be carried out on PCT/US99/22520.

The Preliminary Examination Fee and the handling fee amounting to EUR 1681 are to be debited from our EPO deposit account number 2805.0053 in the name of Wyeth Laboratories Patent Department.

A form 1037 is enclosed with the confirmatory copy for acknowledging receipt.

Yours faithfully

Dr D F Wileman  
European Patent Attorney (GA 34448)



## PCT

## FEE CALCULATION SHEET

Annex to the Demand for international preliminary examination

International application No. <b>PCT/US99/22520</b>	For International Preliminary Examining Authority use only									
Applicant's or agent's file reference <b>ACY-33383</b>	Date stamp of the IPEA									
Applicant <b>AMERICAN CYANAMID COMPANY et al</b>										
<b>Calculation of prescribed fees</b>										
1. Preliminary examination fee .....	<b>EUR 1533</b>	<input type="checkbox"/> P								
2. Handling fee ( <i>Applicants from certain States are entitled to a reduction of 75% of the handling fee. Where the applicant is (or all applicants are) so entitled, the amount to be entered at H is 25% of the handling fee.</i> ) .....	<b>EUR 148</b>	<input type="checkbox"/> H								
3. Total of prescribed fees Add the amounts entered at P and H and enter total in the TOTAL box .....	<b>EUR 1681</b>									
<b>TOTAL</b>										
<b>Mode of Payment</b>										
<table style="width: 100%;"> <tr> <td><input checked="" type="checkbox"/> authorization to charge deposit account with the IPEA (see below)</td> <td><input type="checkbox"/> cash</td> </tr> <tr> <td><input type="checkbox"/> cheque</td> <td><input type="checkbox"/> revenue stamps</td> </tr> <tr> <td><input type="checkbox"/> postal money order</td> <td><input type="checkbox"/> coupons</td> </tr> <tr> <td><input type="checkbox"/> bank draft</td> <td><input type="checkbox"/> other (specify):</td> </tr> </table>			<input checked="" type="checkbox"/> authorization to charge deposit account with the IPEA (see below)	<input type="checkbox"/> cash	<input type="checkbox"/> cheque	<input type="checkbox"/> revenue stamps	<input type="checkbox"/> postal money order	<input type="checkbox"/> coupons	<input type="checkbox"/> bank draft	<input type="checkbox"/> other (specify):
<input checked="" type="checkbox"/> authorization to charge deposit account with the IPEA (see below)	<input type="checkbox"/> cash									
<input type="checkbox"/> cheque	<input type="checkbox"/> revenue stamps									
<input type="checkbox"/> postal money order	<input type="checkbox"/> coupons									
<input type="checkbox"/> bank draft	<input type="checkbox"/> other (specify):									
<b>Deposit Account Authorization</b> ( <i>this mode of payment may not be available at all IPEAs</i> )										
The IPEA/ EP <input checked="" type="checkbox"/> is hereby authorized to charge the total fees indicated above to my deposit account.										
<input checked="" type="checkbox"/> ( <i>this check-box may be marked only if the conditions for deposit accounts of the IPEA so permit</i> ) is hereby authorized to charge any deficiency or credit any overpayment in the total fees indicated above to my deposit account.										
<b>2805.0053</b>	<b>19 April 2000</b>									
Deposit Account Number	Date (day/month/year)	Signature								

The demand must be filed directly with the competent International Preliminary Examining Authority or, if two or more Authorities are competent, with the one chosen by the applicant. The full name or two-letter code of that Authority may be indicated by the applicant on the line below:

IPEA/ EP

# PCT

## CHAPTER II

### DEMAND

under Article 31 of the Patent Cooperation Treaty:

The undersigned requests that the international application specified below be the subject of international preliminary examination according to the Patent Cooperation Treaty and hereby elects all eligible States (except where otherwise indicated).

For International Preliminary Examining Authority use only

Identification of IPEA		Date of receipt of DEMAND
<b>Box No. I IDENTIFICATION OF THE INTERNATIONAL APPLICATION</b>		Applicant's or agent's file reference 33383-00 PCT
International application No. PCT/US99/22520	International filing date (day/month/year) 30 September 1999 ( 30/09/1999 )	(Earliest) Priority date (day/month/year) 30 September 1998 ( 30/09/1998 )
Title of invention MUTANT CHOLERA HOLOTOXIN AS AN ADJUVANT		
<b>Box No. II APPLICANT(S)</b>		
Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.) AMERICAN CYANAMID COMPANY a corporation of Maine Five Giralda Farms Madison, New Jersey 07940 United States of America		Telephone No.: (973) 683-2157
		Facsimile No.: (973) 683-4117
		Teleprinter No.:
State (that is, country) of nationality: UNITED STATES OF AMERICA		State (that is, country) of residence: UNITED STATES OF AMERICA
Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.) THE GOVERNMENT OF THE UNITED STATES OF AMERICA as represented by the UNIFORMED SERVICES UNIVERSITY OF HEALTH SERVICES 4301 Jones Bridge Road Bethesda, Maryland 20814-4799 United States of America		
State (that is, country) of nationality: UNITED STATES OF AMERICA		State (that is, country) of residence: UNITED STATES OF AMERICA
Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.) HOLMES, Randall K. 23371 Morning Rose Drive Golden, Colorado 80401 United States of America		
State (that is, country) of nationality: UNITED STATES OF AMERICA		State (that is, country) of residence: UNITED STATES OF AMERICA
<input checked="" type="checkbox"/> Further applicants are indicated on a continuation sheet.		

## Continuation of Box No. II APPLICANT(S)

*If none of the following sub-boxes is used, this sheet is not to be included in the demand.*

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

JOBLING, Michael G.  
5250 Cherry Creek Drive South, Apt. 18A  
Denver, Colorado 80222  
United States of America

State *(that is, country)* of nationality:

UNITED KINGDOM

State *(that is, country)* of residence:

UNITED STATES OF AMERICA

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

ELDRIDGE, John H.  
4 Beatrice Cove  
Fairport, New York 14450  
United States of America

State *(that is, country)* of nationality:

UNITED STATES OF AMERICA

State *(that is, country)* of residence:

UNITED STATES OF AMERICA

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

GREEN, Bruce A.  
49 Northfield Gate  
Pittsford, New York 14534  
United States of America

State *(that is, country)* of nationality:

UNITED STATES OF AMERICA

State *(that is, country)* of residence:

UNITED STATES OF AMERICA

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

HANCOCK, Gerald E.  
50 Plains Road  
Honeoye Falls, New York 14472  
United States of America

State *(that is, country)* of nationality:

UNITED STATES OF AMERICA

State *(that is, country)* of residence:

UNITED STATES OF AMERICA



Further applicants are indicated on another continuation sheet.

## Continuation of Box No. II APPLICANT(S)

*If none of the following sub-boxes is used, this sheet is not to be included in the demand.*

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

PEEK, Joel A.  
156 Railroad Mills Road  
Pittsford, New York 14534  
United States of America

State *(that is, country)* of nationality:  
UNITED STATES OF AMERICA

State *(that is, country)* of residence:  
UNITED STATES OF AMERICA

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

State *(that is, country)* of nationality:

State *(that is, country)* of residence:

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

State *(that is, country)* of nationality:

State *(that is, country)* of residence:

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

State *(that is, country)* of nationality:

State *(that is, country)* of residence:

☐

Further applicants are indicated on another continuation sheet.

**Box No. III AGENT OR COMMON REPRESENTATIVE; OR ADDRESS FOR CORRESPONDENCE**

The following person is ☒ agent ☐ common representative  
 and ☒ has been appointed earlier and represents the applicant(s) also for international preliminary examination.  
☐ is hereby appointed and any earlier appointment of (an) agent(s) /common representative is hereby revoked.  
☐ is hereby appointed, specifically for the procedure before the International Preliminary Examining Authority, in addition to the agent(s)/common representative appointed earlier.

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

WILEMAN, David F.; CONNELLY, Michael J.; MANNION, Sally K.;  
 TALBOTT, Dawn J.; WALTERS, Philip Bernard Williams  
 WYETH LABORATORIES  
 Huntercombe Lane South  
 Taplow, Maidenhead  
 Berks SL6 0PH  
 United Kingdom

Telephone No.:  
(0628) 604377

Facsimile No.:  
(0628) 799098

Teleprinter No.:

☐ Address for correspondence: Mark this check-box where no agent or common representative is/has been appointed and the space above is used instead to indicate a special address to which correspondence should be sent.

**Box No. IV BASIS FOR INTERNATIONAL PRELIMINARY EXAMINATION****Statement concerning amendments:\***

1. The applicant wishes the international preliminary examination to start on the basis of:

- ☒ the international application as originally filed
- the description ☒ as originally filed  
☐ as amended under Article 34
- the claims ☒ as originally filed  
☐ as amended under Article 19 (together with any accompanying statement)  
☐ as amended under Article 34
- the drawings ☒ as originally filed  
☐ as amended under Article 34

2. ☐ The applicant wishes any amendment to the claims under Article 19 to be considered as reversed.

3. ☐ The applicant wishes the start of the international preliminary examination to be postponed until the expiration of 20 months from the priority date unless the International Preliminary Examining Authority receives a copy of any amendments made under Article 19 or a notice from the applicant that he does not wish to make such amendments (Rule 69.1(d)). *(This check-box may be marked only where the time limit under Article 19 has not yet expired.)*

\* Where no check-box is marked, international preliminary examination will start on the basis of the international application as originally filed or, where a copy of amendments to the claims under Article 19 and/or amendments of the international application under Article 34 are received by the International Preliminary Examining Authority before it has begun to draw up a written opinion or the international preliminary examination report, as so amended.

Language for the purposes of international preliminary examination: ENGLISH

- ☒ which is the language in which the international application was filed.  
☐ which is the language of a translation furnished for the purposes of international search.  
☐ which is the language of publication of the international application.  
☐ which is the language of the translation (to be) furnished for the purposes of international preliminary examination.

**Box No. V ELECTION OF STATES**

The applicant hereby elects all eligible States *(that is, all States which have been designated and which are bound by Chapter II of the PCT)*

excluding the following States which the applicant wishes not to elect:

**Box No. VI CHECK LIST**

The demand is accompanied by the following elements, in the language referred to in Box No. IV, for the purposes of international preliminary examination:

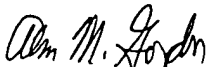
			For International Preliminary Examining Authority use only	
			received	not received
1.	translation of international application	sheets	<input type="checkbox"/>	<input type="checkbox"/>
2.	amendments under Article 34	sheets	<input type="checkbox"/>	<input type="checkbox"/>
3.	copy (or, where required, translation) of amendments under Article 19	sheets	<input type="checkbox"/>	<input type="checkbox"/>
4.	copy (or, where required, translation) of statement under Article 19	sheets	<input type="checkbox"/>	<input type="checkbox"/>
5.	letter	sheets	<input type="checkbox"/>	<input type="checkbox"/>
6.	other ( <i>specify</i> )	sheets	<input type="checkbox"/>	<input type="checkbox"/>

The demand is also accompanied by the item(s) marked below:

- |  |   |
|--|---|
| 1. <input checked="" type="checkbox"/> fee calculation sheet                             | 4. <input type="checkbox"/> statement explaining lack of signature                                  |
| 2. <input type="checkbox"/> separate signed power of attorney                            | 5. <input type="checkbox"/> nucleotide and or amino acid sequence listing in computer readable form |
| 3. <input type="checkbox"/> copy of general power of attorney; reference number, if any: | 6. <input type="checkbox"/> other ( <i>specify</i> ):   |

**Box No. VII SIGNATURE OF APPLICANT, AGENT OR COMMON REPRESENTATIVE**

Next to each signature, indicate the name of the person signing and the capacity in which the person signs (if such capacity is not obvious from reading the demand).



ALAN M. GORDON  
AGENT FOR APPLICANTS

For International Preliminary Examining Authority use only

- Date of actual receipt of DEMAND:
- Adjusted date of receipt of demand due to CORRECTIONS under Rule 60.1(b):
- ☐ The date of receipt of the demand is AFTER the expiration of 19 months from the priority date and item 4 or 5, below, does not apply.
 ☐ The applicant has been informed accordingly.
- ☐ The date of receipt of the demand is WITHIN the period of 19 months from the priority date as extended by virtue of Rule 80.5.
- ☐ Although the date of receipt of the demand is after the expiration of 19 months from the priority date, the delay in arrival is EXCUSED pursuant to Rule 82.

For International Bureau use only

Demand received from IPEA on:

# JOINT COOPERATION TREATY

FEB 28 2000

From the INTERNATIONAL SEARCHING AUTHORITY

**PCT**

NOTIFICATION OF TRANSMITTAL OF  
THE INTERNATIONAL SEARCH REPORT  
OR THE DECLARATION

(PCT Rule 44.1)

To:  
AMERICAN HOME PRODUCTS CORPORATION  
Attn. Gordon, Alan M.  
Patent Law Department -2B2  
One Campus Drive  
Parsippany, New Jersey, 07054  
UNITED STATES OF AMERICA

Date of mailing  
(day/month/year) 14/02/2000

Applicant's or agent's file reference

33383-00 PCT

**FOR FURTHER ACTION** See paragraphs 1 and 4 below

International application No.

PCT/US 99/22520

International filing date

(day/month/year) 30/09/1999

Applicant

AMERICAN CYANAMID COMPANY et al.

1. ☒ The applicant is hereby notified that the International Search Report has been established and is transmitted herewith.

**Filing of amendments and statement under Article 19:**

The applicant is entitled, if he so wishes, to amend the claims of the International Application (see Rule 46):

**When?** The time limit for filing such amendments is normally 2 months from the date of transmittal of the International Search Report; however, for more details, see the notes on the accompanying sheet.

**Where?** Directly to the International Bureau of WIPO  
34, chemin des Colombettes  
1211 Geneva 20, Switzerland  
Facsimile No.: (41-22) 740.14.35

For more detailed instructions, see the notes on the accompanying sheet.

2. ☐ The applicant is hereby notified that no International Search Report will be established and that the declaration under Article 17(2)(a) to that effect is transmitted herewith.

3. ☐ With regard to the protest against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

☐ the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.

☐ no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. **Further action(s):** The applicant is reminded of the following:

Shortly after 18 months from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau as provided in Rules 90bis.1 and 90bis.3, respectively, before the completion of the technical preparations for international publication.

Within 19 months from the priority date, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase until 30 months from the priority date (in some Offices even later).

Within 20 months from the priority date, the applicant must perform the prescribed acts for entry into the national phase before all designated Offices which have not been elected in the demand or in a later election within 19 months from the priority date or could not be elected because they are not bound by Chapter II.

Name and mailing address of the International Searching Authority



European Patent Office, P.B. 5818 Patentlaan 2  
NL-2280 HV Rijswijk  
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,  
Fax: (+31-70) 340-3016

Authorized officer

Nina Vercio

CO: TAPLOW



## NOTES TO FORM PCT/ISA/220

These Notes are intended to give the basic instructions concerning the filing of amendments under article 19. The Notes are based on the requirements of the Patent Cooperation Treaty, the Regulations and the Administrative Instructions under that Treaty. In case of discrepancy between these Notes and those requirements, the latter are applicable. For more detailed information, see also the PCT Applicant's Guide, a publication of WIPO.

In these Notes, "Article", "Rule", and "Section" refer to the provisions of the PCT, the PCT Regulations and the PCT Administrative Instructions respectively.

### INSTRUCTIONS CONCERNING AMENDMENTS UNDER ARTICLE 19

The applicant has, after having received the international search report, one opportunity to amend the claims of the international application. It should however be emphasized that, since all parts of the international application (claims, description and drawings) may be amended during the international preliminary examination procedure, there is usually no need to file amendments of the claims under Article 19 except where, e.g. the applicant wants the latter to be published for the purposes of provisional protection or has another reason for amending the claims before international publication. Furthermore, it should be emphasized that provisional protection is available in some States only.

#### What parts of the international application may be amended?

Under Article 19, only the claims may be amended.

During the international phase, the claims may also be amended (or further amended) under Article 34 before the International Preliminary Examining Authority. The description and drawings may only be amended under Article 34 before the International Examining Authority.

Upon entry into the national phase, all parts of the international application may be amended under Article 28 or, where applicable, Article 41.

#### When?

Within 2 months from the date of transmittal of the international search report or 16 months from the priority date, whichever time limit expires later. It should be noted, however, that the amendments will be considered as having been received on time if they are received by the International Bureau after the expiration of the applicable time limit but before the completion of the technical preparations for international publication (Rule 46.1).

#### Where not to file the amendments?

The amendments may only be filed with the International Bureau and not with the receiving Office or the International Searching Authority (Rule 46.2).

Where a demand for international preliminary examination has been/is filed, see below.

#### How?

Either by cancelling one or more entire claims, by adding one or more new claims or by amending the text of one or more of the claims as filed.

A replacement sheet must be submitted for each sheet of the claims which, on account of an amendment or amendments, differs from the sheet originally filed.

All the claims appearing on a replacement sheet must be numbered in Arabic numerals. Where a claim is cancelled, no renumbering of the other claims is required. In all cases where claims are renumbered, they must be renumbered consecutively (Administrative Instructions, Section 205(b)).

The amendments must be made in the language in which the international application is to be published.

#### What documents must/may accompany the amendments?

**Letter (Section 205(b)):**

The amendments must be submitted with a letter.

The letter will not be published with the international application and the amended claims. It should not be confused with the "Statement under Article 19(1)" (see below, under "Statement under Article 19(1)").

The letter must be in English or French, at the choice of the applicant. However, if the language of the international application is English, the letter must be in English; if the language of the international application is French, the letter must be in French.

## NOTES TO FORM PCT/ISA/220 (continued)

The letter must indicate the differences between the claims as filed and the claims as amended. It must, in particular, indicate, in connection with each claim appearing in the international application (it being understood that identical indications concerning several claims may be grouped), whether

- (i) the claim is unchanged;
- (ii) the claim is cancelled;
- (iii) the claim is new;
- (iv) the claim replaces one or more claims as filed;
- (v) the claim is the result of the division of a claim as filed.

The following examples illustrate the manner in which amendments must be explained in the accompanying letter:

1. [Where originally there were 48 claims and after amendment of some claims there are 51]:  
"Claims 1 to 29, 31, 32, 34, 35, 37 to 48 replaced by amended claims bearing the same numbers; claims 30, 33 and 36 unchanged; new claims 49 to 51 added."
2. [Where originally there were 15 claims and after amendment of all claims there are 11]:  
"Claims 1 to 15 replaced by amended claims 1 to 11."
3. [Where originally there were 14 claims and the amendments consist in cancelling some claims and in adding new claims]:  
"Claims 1 to 6 and 14 unchanged; claims 7 to 13 cancelled; new claims 15, 16 and 17 added." or  
"Claims 7 to 13 cancelled; new claims 15, 16 and 17 added; all other claims unchanged."
4. [Where various kinds of amendments are made]:  
"Claims 1-10 unchanged; claims 11 to 13, 18 and 19 cancelled; claims 14, 15 and 16 replaced by amended claim 14; claim 17 subdivided into amended claims 15, 16 and 17; new claims 20 and 21 added."

### "Statement under article 19(1)" (Rule 46.4)

The amendments may be accompanied by a statement explaining the amendments and indicating any impact that such amendments might have on the description and the drawings (which cannot be amended under Article 19(1)).

The statement will be published with the international application and the amended claims.

It must be in the language in which the international application is to be published.

It must be brief, not exceeding 500 words if in English or if translated into English.

It should not be confused with and does not replace the letter indicating the differences between the claims as filed and as amended. It must be filed on a separate sheet and must be identified as such by a heading, preferably by using the words "Statement under Article 19(1)."

It may not contain any disparaging comments on the international search report or the relevance of citations contained in that report. Reference to citations, relevant to a given claim, contained in the international search report may be made only in connection with an amendment of that claim.

### Consequence if a demand for international preliminary examination has already been filed

If, at the time of filing any amendments under Article 19, a demand for international preliminary examination has already been submitted, the applicant must preferably, at the same time of filing the amendments with the International Bureau, also file a copy of such amendments with the International Preliminary Examining Authority (see Rule 62.2(a), first sentence).

### Consequence with regard to translation of the international application for entry into the national phase

The applicant's attention is drawn to the fact that, where upon entry into the national phase, a translation of the claims as amended under Article 19 may have to be furnished to the designated/elected Offices, instead of, or in addition to, the translation of the claims as filed.

For further details on the requirements of each designated/elected Office, see Volume II of the PCT Applicant's Guide.

# PATENT COOPERATION TREATY

## PCT

### INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference <b>33383-00 PCT</b>	<b>FOR FURTHER ACTION</b> see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
International application No. <b>PCT/US 99/ 22520</b>	International filing date (day/month/year) <b>30/09/1999</b>	(Earliest) Priority Date (day/month/year) <b>30/09/1998</b>
Applicant  <b>AMERICAN CYANAMID COMPANY et al.</b>		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 5 sheets.

☒ It is also accompanied by a copy of each prior art document cited in this report.

#### 1. Basis of the report

a. With regard to the language, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

☐ the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

b. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international search was carried out on the basis of the sequence listing :

☐ contained in the international application in written form.

☐ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority in written form.

☐ furnished subsequently to this Authority in computer readable form.

☐ the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

☐ the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. ☒ Certain claims were found unsearchable (See Box I).

3. ☐ Unity of invention is lacking (see Box II).

4. With regard to the title,

☒ the text is approved as submitted by the applicant.

☐ the text has been established by this Authority to read as follows:

5. With regard to the abstract,

☒ the text is approved as submitted by the applicant.

☐ the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the drawings to be published with the abstract is Figure No.

☐ as suggested by the applicant.

☐ because the applicant failed to suggest a figure.

☐ because this figure better characterizes the invention.

☒ None of the figures.

# INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 99/22520

## Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 17-23  
because they relate to subject matter not required to be searched by this Authority, namely:  
Rule 31.1 (iv) PCT - Method for treatment of the human animal body by therapy
2. ☐ Claims Nos.:  
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

# INTERNATIONAL SEARCH REPORT

Application No

PCT/US 99/22520

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61K39/39 A61K39/095 A61K39/102 A61K39/106 A61K39/245  
A61K39/155 A61K39/15 C12N15/63 C12N5/10 //C07K14/28

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K C07K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 97 29771 A (PIZZA MARIAGRAZIA ;RAPPUOLI RINO (IT); CHIRON SPA (IT); FONTANA MA) 21 August 1997 (1997-08-21) page 4, line 1-25 page 5, line 19,20 page 42, line 5 -page 47, line 20 claims 1,6-8,15	1,2,4-27
Y	---	1-27
Y	GLINEUR C ET AL: "Importance of ADP-ribosylation in the morphological changes of PC12 cells induced by cholera toxin." INFECTION AND IMMUNITY, (1994 OCT) 62 (10) 4176-85. , XP002129167 abstract	1-27
	--- -/--	

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

### \* Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- "&" document member of the same patent family

Date of the actual completion of the international search

1 February 2000

Date of mailing of the international search report

14/02/2000

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2  
NL - 2280 HV Rijswijk  
Tel. (+31-70) 340-2040, T.x. 31 651 epo nl,  
Fax: (+31-70) 340-3016

Authorized officer

Covone, M

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	YAMAMOTO S ET AL: "Mutants in the ADP-ribosyltransferase cleft of cholera toxin lack diarrheagenicity but retain adjuvanticity." JOURNAL OF EXPERIMENTAL MEDICINE, (1997 APR 7) 185 (7) 1203-10. , XP002129168 abstract tables 1,2 page 1209, right-hand column, paragraph 2 ---	1,2,13, 15-17, 24-27
X	WO 97 02348 A (BIOCINE SPA ;PIZZA MARIAGRAZIA (IT); FONTANA MARIA RITA (IT); GIAN) 23 January 1997 (1997-01-23) page 8, line 31 -page 9, line 2 page 11, line 3-6 page 49, line 24 -page 50, line 7 claims 5-7,14 ---	1,2,13, 15-17, 24-27
A	RICHARDS C M ET AL: "Enhancement of the immune response to non-replicating herpes simplex virus type-1 preparations by mucosal administration in the presence of cholera toxin" VACCINE,GB,BUTTERWORTH SCIENTIFIC. GUILDFORD, vol. 15, no. 10, 1 July 1997 (1997-07-01), pages 1065-1069, XP004085964 ISSN: 0264-410X abstract ---	4,11,12, 23
A	NEDRUD J. ET AL: "Oral immunization against respiratory viruses in mice." ADVANCES IN EXPERIMENTAL MEDICINE AND BIOLOGY, (1995) 371/B (1595-1598). , XP000867733 figure 1 ---	4,8,21
A	WO 97 05267 A (MAXIM PHARMACEUTICALS) 13 February 1997 (1997-02-13) page 3, line 13 -page 5, line 24 ---	11,12
P,X	WO 98 45324 A (UAB RESEARCH FOUNDATION ;KIYONO HIROSHI (US); MCGHEE JERRY R (US);) 15 October 1998 (1998-10-15) page 4, line 6 -page 5, line 15 claims --- -/--	1-27

# INTERNATIONAL SEARCH REPORT

In tional Application No  
PCT/US 99/22520

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	<p>ZHU, D. ET AL: "Intragastric immunization with recombinant H. pylori urease formulated with attenuated cholera toxin elicits systemic, mucosal and protective immune responses in C57BL/6 mice." FASEB JOURNAL, (MARCH 12, 1999) VOL. 13, NO. 4 PART 1, PP. A291. MEETING INFO.: ANNUAL MEETING OF THE PROFESSIONAL RESEARCH SCIENTISTS FOR EXPERIMENTAL BIOLOGY 99 WASHINGTON, D.C., USA APRIL 17-21, 1999 , XP000867558 the whole document -----</p>	1-27

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 99/22520

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9729771 A	21-08-1997	CA 2244800 A EP 0880361 A	21-08-1997 02-12-1998
WO 9702348 A	23-01-1997	AU 6238896 A EP 0835314 A	05-02-1997 15-04-1998
WO 9705267 A	13-02-1997	AU 6505796 A EP 0840796 A JP 11510164 T	26-02-1997 13-05-1998 07-09-1999
WO 9845324 A	15-10-1998	NONE	



# PATENT COOPERATION TREATY

## PCT

### INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 33383-00 PCT	<b>FOR FURTHER ACTION</b> See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)	
International application No. PCT/US99/22520	International filing date (day/month/year) 30/09/1999	Priority date (day/month/year) 30/09/1998
International Patent Classification (IPC) or national classification and IPC A61K39/39		
Applicant AMERICAN CYANAMID COMPANY et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.


2. This REPORT consists of a total of 8 sheets, including this cover sheet.

☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

- I ☒ Basis of the report
- II ☐ Priority
- III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☒ Certain documents cited
- VII ☒ Certain defects in the international application
- VIII ☒ Certain observations on the international application

Date of submission of the demand 19/04/2000	Date of completion of this report 07.12.2000
Name and mailing address of the international preliminary examining authority:  European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer  Weaver, M  Telephone No. +49 89 2399 8689



**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT**

International application No. PCT/US99/22520

**I. Basis of the report**

1. This report has been drawn on the basis of *(substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments (Rules 70.16 and 70.17).)*:

**Description, pages:**

1-117 as originally filed

**Claims, No.:**

1-27 as originally filed

**Drawings, sheets:**

1/21-21/21 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:

**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT**

International application No. PCT/US99/22520

☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

*(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)*

6. Additional observations, if necessary:

**III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability**

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application.

☒ claims Nos. 17 - 23.

because:

☒ the said international application, or the said claims Nos. 17 -23 with respect to industrial applicability relate to the following subject matter which does not require an international preliminary examination (*specify*):  
**see separate sheet**

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the said claims Nos. .

2. A meaningful international preliminary examination report cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

☐ the written form has not been furnished or does not comply with the standard.

☐ the computer readable form has not been furnished or does not comply with the standard.

**V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. Statement

Novelty (N)

Yes: Claims 2-27

**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT**

International application No. PCT/US99/22520

	No:	Claims	1
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-27
Industrial applicability (IA)	Yes:	Claims	1-16, 24-27
	No:	Claims	

2. Citations and explanations  
**see separate sheet**

**VI. Certain documents cited**

1. Certain published documents (Rule 70.10)

and / or

2. Non-written disclosures (Rule 70.9)

**see separate sheet**

**VII. Certain defects in the international application**

The following defects in the form or contents of the international application have been noted:  
**see separate sheet**

**VIII. Certain observations on the international application**

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:  
**see separate sheet**

**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/US99/22520

**Section III**

Claims 17 - 23 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

**Section V**

1. Claim 1 contains the disclaimer "has a substitution other than aspartic acid for the glutamic acid at position 29 of the A subunit of the cholera toxin". The wording chosen means that the subject-matter of claim 1 encompasses any substitution other than D29E, including substitutions at positions other than 29 of CT-A, provided that the resultant cholera holotoxin has reduced toxicity compared to the wild type but retains immunogenicity.
2. As antigenic compositions containing a mutant cholera holotoxin as adjuvant and which fall within the scope of claim 1 are known from **D1 (WO-A-97/29771)**; page 4, lines 29 - 31; page 5, lines 19/20; page 10, lines 2 - 5; page 11, lines 10 - 13; page 45, line 16 - page 46, line 24; claim 15) with respect to a P106S mutant used as adjuvant for tetanus toxin, and **D2 (WO-A-97/02348)**; abstract; page 8, line 20 - page 9, line 13; page 10, line 36 - page 11, line 6; page 49, line 24 - page 50, line 17; claims 4, 14), claim 1 lacks novelty and does not meet the requirements of Article 33(2) PCT.
3. Moreover, the use of a cholera toxin containing the S61F or E112K mutation as a mucosal adjuvant is clearly suggested in **D3 (J Exp Med 185 (1997) 1203)**; summary; page 1209, column 2, lines 12 - 24; Tables 1 and 2).  
  
Claim 1 is thus considered to lack an inventive step over the disclosure of D3 (Article 33(3) PCT).
4. Dependent claims 2 - 16 do not contain any features which, in combination with the features of any claim to which they refer, meet the requirements of the PCT in respect of novelty or inventive step, the reasons being as follows:

**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/US99/22520

Claim 2: Mutated CT-A is itself an antigen such that this claim lacks novelty over the disclosure of D1 or D2;

Claim 3: Numerous CT-A point mutations are known to result in reduced toxicity while retaining immunogenicity (see e.g. page 4, lines 1 - 12 of D1). The choice of the particular E29H mutation would thus not appear to be inventive as the skilled person would be motivated to look for other "non-toxic, immunogenic" mutations in addition to those already known. Moreover, position 29 is a known mutation site (see Infect Immun 62 (1994) 4176; abstract));

Claims 4 - 12: The choice of a particular antigen against which antibodies are to be raised cannot render an obvious adjuvant inventive;

Claims 13, 14: The skilled person would regard it as a normal option to include the further features of these claims;

Claims 15, 16: Double CT-A mutants are known in the art (see e.g. D1, pages 4, lines 1 - 18; D2 and D3).

5. The use of the mutant CT-A of any of claims 1 - 15 as an adjuvant is considered to lack an inventive step over the disclosures of D1 - D3, for the reasons set out in points 1 - 4 above. Method claims 17 - 23 and use claim 27 therefore do not meet the requirements of Article 33(3) PCT.
6. A plasmid containing a known promoter together with a sequence encoding the mutant CT-A of claim 1, a host cell transformed, transduced or transfected with the plasmid and the method of preparing the mutant cholera holotoxin using the said plasmid and host cells all lack inventive step over the disclosures of D1 - D3 for the reasons set out above in the light of the further disclosures in D1 - D3 on e.g. page 19, line 20 - page 41, line 3 of D1; page 22, line 5 - page 44, line 27 of D2; D3: "Materials and Methods".

Claims 24 - 26 therefore do not meet the requirements of Article 33(3) PCT.

7. For the assessment of the present claims 17 - 23 on the question whether they

**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/US99/22520

are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognise as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

**Section VI**

Certain published documents (Rule 70.10)

Certain published documents (Rule 70.10)

Application No Patent No	Publication date (day/month/year)	Filing date (day/month/year)	Priority date (valid claim) (day/month/year)
WO-A-98/45324	15.10.1998	03.04.1998	04.04.1997*

\* Validity not verified

**Section VII**

Contrary to the requirements of Rule 5.1(a)(ii) PCT, the relevant background art disclosed in the documents D1 - D3 is not mentioned in the description, nor are these documents identified therein.

**Section VIII**

1. At least claims 1 and 2 and the claims which refer to these claims lack clarity (Article 6 PCT), as they contain a disclaimer (see Section V, point 1), although the subject-matter which is both sufficiently disclosed and supported by the description (see point 2 below) can be defined more clearly and concisely in terms of positive features (see also the PCT Guidelines Ch. III-4.12).
2. Claims 1,2 and 4 - 24 are not supported by the description as required by Article 6 PCT, as their scope is broader than justified by the description and drawings. The reasons therefor are the following:

**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT - SEPARATE SHEET**

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International application No. PCT/US99/22520

The sole concrete experimental disclosure in the application as filed is with respect to the E29H mutation. In fact, all of the examples refer to this mutant only (page 8, line 19 - page 9, line 19; page 10, line 13 - page 36, line 10; page 42, lines 3 - 30 and all Examples and Tables).

3. Claims 1, 2 and 4 - 24 relate to any possible CT-A point mutation at any possible position, or any combination thereof, provided none of these mutations are E29D. There is, however, no evidence in the application to show that all of these possibilities both retain immunogenicity/adjuvanticity and have reduced toxicity. Moreover, it is exceedingly unlikely that this would be the case, given that a CT-A having all of its amino acids mutated is also included in the scope of the "mutant cholera holotoxin" (see also the wording of claim 15 in this context).

These claims thus do not meet the requirements of Article 5 PCT over their whole scope.



# PATENT COOPERATION TREATY

## PCT

### INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference <b>33383-00 PCT</b>	<b>FOR FURTHER ACTION</b> <small>see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.</small>	
International application No. <b>PCT/US 99/ 22520</b>	International filing date (day/month/year) <b>30/09/1999</b>	(Earliest) Priority Date (day/month/year) <b>30/09/1998</b>
Applicant  <b>AMERICAN CYANAMID COMPANY et al.</b>		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 5 sheets.

☒ It is also accompanied by a copy of each prior art document cited in this report.

**1. Basis of the report**

a. With regard to the **language**, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

☐ the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

☐ contained in the international application in written form.

☐ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority in written form.

☐ furnished subsequently to this Authority in computer readable form.

☐ the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

☐ the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. ☒ **Certain claims were found unsearchable** (See Box I).

3. ☐ **Unity of invention is lacking** (see Box II).

4. With regard to the **title**,

☒ the text is approved as submitted by the applicant.

☐ the text has been established by this Authority to read as follows:

5. With regard to the **abstract**,

☒ the text is approved as submitted by the applicant.

☐ the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No.

☐ as suggested by the applicant.

☐ because the applicant failed to suggest a figure.

☐ because this figure better characterizes the invention.

☒ None of the figures.

# INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 99/22520

## Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 17-23  
because they relate to subject matter not required to be searched by this Authority, namely:  
Rule 31.1 (iv) PCT - Method for treatment of the human animal body by therapy
2. ☐ Claims Nos.:  
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

# INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 99/22520

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61K39/39 A61K39/095 A61K39/102 A61K39/106 A61K39/245  
A61K39/155 A61K39/15 C12N15/63 C12N5/10 //C07K14/28

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K C07K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 97 29771 A (PIZZA MARIAGRAZIA ;RAPPUOLI RINO (IT); CHIRON SPA (IT); FONTANA MA) 21 August 1997 (1997-08-21) page 4, line 1-25 page 5, line 19,20 page 42, line 5 -page 47, line 20 claims 1,6-8,15	1,2,4-27
Y	---	1-27
Y	GLINEUR C ET AL: "Importance of ADP-ribosylation in the morphological changes of PC12 cells induced by cholera toxin." INFECTION AND IMMUNITY, (1994 OCT) 62 (10) 4176-85. , XP002129167 abstract	1-27
	---	
	-/--	

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

### \* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

1 February 2000

Date of mailing of the international search report

14/02/2000

Name and mailing address of the ISA

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Fax: (+31-70) 340-3016

Authorized officer

Covone, M

# INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 99/22520

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	YAMAMOTO S ET AL: "Mutants in the ADP-ribosyltransferase cleft of cholera toxin lack diarrheagenicity but retain adjuvant activity." JOURNAL OF EXPERIMENTAL MEDICINE, (1997 APR 7) 185 (7) 1203-10. , XP002129168 abstract tables 1,2 page 1209, right-hand column, paragraph 2 ---	1,2,13, 15-17, 24-27
X	WO 97 02348 A (BIOCINE SPA ;PIZZA MARIAGRAZIA (IT); FONTANA MARIA RITA (IT); GIAN) 23 January 1997 (1997-01-23) page 8, line 31 -page 9, line 2 page 11, line 3-6 page 49, line 24 -page 50, line 7 claims 5-7,14 ---	1,2,13, 15-17, 24-27
A	RICHARDS C M ET AL: "Enhancement of the immune response to non-replicating herpes simplex virus type-1 preparations by mucosal administration in the presence of cholera toxin" VACCINE,GB,BUTTERWORTH SCIENTIFIC. GUILDFORD, vol. 15, no. 10, 1 July 1997 (1997-07-01), pages 1065-1069, XP004085964 ISSN: 0264-410X abstract ---	4,11,12, 23
A	NEDRUD J. ET AL: "Oral immunization against respiratory viruses in mice." ADVANCES IN EXPERIMENTAL MEDICINE AND BIOLOGY, (1995) 371/B (1595-1598). , XP000867733 figure 1 ---	4,8,21
A	WO 97 05267 A (MAXIM PHARMACEUTICALS) 13 February 1997 (1997-02-13) page 3, line 13 -page 5, line 24 ---	11,12
P,X	WO 98 45324 A (UAB RESEARCH FOUNDATION ;KIYONO HIROSHI (US); MCGHEE JERRY R (US);) 15 October 1998 (1998-10-15) page 4, line 6 -page 5, line 15 claims ---	1-27
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# INTERNATIONAL SEARCH REPORT

In .tional Application No

PCT/US 99/22520

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	<p>ZHU, D. ET AL: "Intragastric immunization with recombinant H. pylori urease formulated with attenuated cholera toxin elicits systemic, mucosal and protective immune responses in C57BL/6 mice." FASEB JOURNAL, (MARCH 12, 1999) VOL. 13, NO. 4 PART 1, PP. A291. MEETING INFO.: ANNUAL MEETING OF THE PROFESSIONAL RESEARCH SCIENTISTS FOR EXPERIMENTAL BIOLOGY 99 WASHINGTON, D.C., USA APRIL 17-21, 1999 , XP000867558 the whole document.</p> <p>-----</p>	1-27

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 99/22520

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9729771 A	21-08-1997	CA 2244800 A EP 0880361 A	21-08-1997 02-12-1998
WO 9702348 A	23-01-1997	AU 6238896 A EP 0835314 A	05-02-1997 15-04-1998
WO 9705267 A	13-02-1997	AU 6505796 A EP 0840796 A JP 11510164 T	26-02-1997 13-05-1998 07-09-1999
WO 9845324 A	15-10-1998	NONE	